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Attenuation of ischemic liver injury by monoclonal anti-endothelin antibody, AwETN40.

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BACKGROUND: Enhanced production of endothelin-1 (ET-1), vasoconstrictive 21 amino acids produced by endothelial cells during ischemia and after reperfusion of the liver, is known to cause sinusoidal constriction and microcirculatory disturbances, which lead to severe tissue damage. Using a 2-hour hepatic vascular exclusion model in dogs, we tested our hypothesis that neutralization of ET-1 by monoclonal anti-ET-1 and anti-ET-2 antibody (AwETN40) abates vascular dysfunction and ameliorates ischemia/reperfusion injury of the liver. STUDY DESIGN: After skeletonization, the liver was made totally ischemic by cross-clamping the portal vein, the hepatic artery, and the vena cava (above and below the liver). Veno-venous bypass was used to decompress splanchnic and inferior systemic congestion. AwETN40, 5 mg/kg, was administered intravenously 10 minutes before ischemia (treatment group, n = 5). Nontreated animals were used as controls (control group, n = 10). Animal survival, hepatic tissue blood flow, liver function tests, total bile acid, high-energy phosphate, ET-1 levels, and liver histopathology were studied. RESULTS: Treatment with AwETN40 improved 2-week animal survival from 30% to 100%. Hepatic tissue blood flow after reperfusion was significantly higher in the treatment group. The treatment significantly attenuated liver enzyme release, total bile acid, and changes in adenine nucleotides. Immunoreactive ET-1 levels in the hepatic venous blood of the control group showed a significant increase and remained high for up to 24 hours after reperfusion. Histopathologic alterations were significantly lessened in the treatment group. CONCLUSIONS: These results indicate that ET-1 is involved in ischemia/reperfusion injury of the liver, which can be ameliorated by the monoclonal anti-ET-1 and anti-ET-2 antibody AwETN40.

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